IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorn y Dock t No. 71007/137/USGO

In re patent application of
Apurba BHATTACHARJEE *et al.*
Serial No. 08/230,402
Filed: April 20, 1994
For: VACCINE AGAINST GRAM-NEGATIVE BACTERIAL INFECTIONS

Group Art Unit: 1802
Examiner: H. Sidberry

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Alan S. Cross, M.D., declare and say as follows:

1. I am the Alan S. Cross shown as coinventor on the captioned patent application.

2. I have had twenty three years of experience in the field of vaccines directed against bacterial infections. My *curriculum vita* is enclosed.

3. I have read in detail Examiner Paper No. 13, an Office Action in the captioned application mailed October 29, 1996 by Examiner H. Sidberry.

4. In my opinion, there is no basis for the Examiner's assertions that Zollinger *et al.*, United States Patent No. 4,707,543 anticipates or makes obvious the present invention; the differences are striking at every level, as I will outline below:

4.1. In lines 4-5 of the Zollinger Abstract, it is stated that the patent is to products useful as vaccines against infection ". . . by the <u>same</u> bacteria" . . . and protecting . . . against the <u>same</u> infection . . ." (emphasis added)

In sharp contrast, our vaccine protects against heterologous infections. See, Example 10, p.20 and Example 11, p.22. This is now a limitation on all claims.

4.2 Zollinger is concerned with the interaction of vaccine components with the homologous bacteria from which the vaccines are derived.

4.3 Zollinger provides no evidence of cross-protection.

4.4 Zollinger provides no evidence of passive immunization, which is a property of the present vaccine.

4.5 Zollinger recites that the LPS portion of the vaccine can be substituted with the LPS of other Gram-negative bacteria, including *E. coli*. Zollinger implies that these LPSs could provide only type-specific protection. In other words, if the LPS were obtained from *E. coli* 018, then it would be effective only against infection with *E. coli* 018. No data is presented on this subject by Zollinger, and no discussion is provided. It would not be apparent from the Zollinger disclosure that the substitution of the meningococcal polysaccharide or LPS with that of *E. coli* would provide heterologous protection.

5. A second element of the claimed invention that is not anticipated or obviousness-making by Zollinger, is the present role of OMP strictly as an adjuvant. OMP induces no protective activity of its own. Rather, it maintains the LPS in a proper spatial configuration such that relevant cross-reactive epitopes are exposed in a manner different then when they simply are conjugated to protein given alone. Thus, the concepts of the protective antibodies are quite different between Zollinger and ourselves.

6. The present type of antibody induced is also different. In the Zollinger patent, what were produced were

bacteriocidal (in the presence of complement) antibodies. The Gram-negative bacilli targeted by the present vaccine are serum-resistant, and antibody against any of their surface components are not bacteriocidal, unlike the case with meningococci. Here too, the Zollinger vaccine would be ineffective against homologous target (i.e., the antibodies induced by *E. coli* 018 LPS plus OMP would not kill 018 subgroup *E. coli*). This is now a limitation on claim 1.

7. In summary, Zollinger's bacteriocidal antibodies have no utility in the treatment of infections with enteric gram-negative bacilli. In the present vaccine, the antibody induced by the vaccine facilitates the clearance of LPS by phagocytic cells within the body.

8. Nowhere in Zollinger is it recognized or stated that antibodies induced by their vaccine either with meningococcal LPS or the LPS from enteric bacilli require the participation of cells within the body to be effective. In other words, based on the data generated with antibodies with our vaccine, there is nothing in Zollinger to anticipate our findings.

9. It is of interest that the examiner dwells on applicants animal model in the Office Action, but neglects to note that her sole reference (Zollinger) does not mention animal models.

10. It is self evident that Zollinger does not anticipate that our vaccines would induce the production of antibodies that would protect a subject from the consequences of uncontrolled heterologous bacterial infection or LPS in the blood.

11. In sum, it is our opinion that only a perverse interpretation of the facts could lead to a finding that Zollinger anticipates our claims to a vaccine that (1) provides <u>heterologous</u> protection; (2) is effective in working with phagocytic cells, and does not rely on the induction of a bacteriocidal antibody; and (3) produces an antibody that is not bacteriocidal.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

Respectfully submitted,

Alan S. Cross

Alan S. Cross, M.D.

3/21/97

Date